

CLAIMS

We Claim:

1. An antimicrobial sulfonamide derivative, or a salt or a hydrate thereof,
5 comprising:

a core cyclic peptide or core antibiotic of a lipopeptide antibiotic; and
a lipophilic moiety,

wherein said lipophilic moiety is covalently attached to the core cyclic peptide or core
cyclic antibiotic *via* a linking chain which includes a sulfonamide linkage.

2. The antimicrobial sulfonamide derivative, salt or hydrate of Claim 1 in which
the linking chain is a sulfonamide linkage.

3. The antimicrobial sulfonamide derivative, salt or hydrate of Claim 1 in which
15 the linking chain is a linker that links the core cyclic peptide or core antibiotic to the lipophilic
moiety.

4. The antimicrobial sulfonamide derivative, salt or hydrate of Claim 1 which is a
compound according to structural Formula (I):



wherein:

Y is a lipophilic moiety;

25 Each X is independently selected from the group consisting of $-\text{CO}-$,
 $-\text{SO}_2-$, $-\text{CS}-$, $-\text{PO}-$, $-\text{OP}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{NHCO}-$ and $-\text{N}(\text{R}^1)\text{CO}-$ with the
proviso that at least one X is $-\text{SO}_2-$;

m is 0 or 1;

L is a linker;

30 N is nitrogen;

R^1 and R^2 are each independently selected from the group consisting of
hydrogen, $(\text{C}_1-\text{C}_{25})$ alkyl optionally substituted with one or more of the same or different R^2

groups, (C₁-C₂₅) heteroalkyl optionally substituted with one or more of the same or different R² groups, (C₅-C₃₀) aryl optionally substituted with one or more of the same or different R² groups, (C₅-C₃₀) arylaryl optionally substituted with one or more of the same or different R² groups, (C₅-C₃₀) biaryl optionally substituted with one or more of the same or different R² groups, five to thirty membered heteroaryl optionally substituted with one or more of the same or different R² groups, (C₆-C₃₀) arylalkyl optionally substituted with one or more of the same or different R² groups and six to thirty membered heteroarylalkyl optionally substituted with one or more of the same or different R² groups;

each R² is independently selected from the group consisting of —OR³, —SR³, —NR³R³, —CN, —NO₂, —N₃, —C(O)OR³, —C(O)NR³R³, —C(S)NR³R³, —C(NR³)NR³R³, —CHO, —R³CO, —SO₂R³, —SOR³, —PO(OR³)₂, —PO(OR³), —CO₂H, —SO₃H, —PO₃H, halogen and trihalomethyl;

each R³ is independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, (C₅-C₁₀) aryl, five to sixteen membered heteroaryl, (C₆-C₁₆) arylalkyl and six to sixteen membered heteroarylalkyl; and

R is a core cyclic peptide or core antibiotic of a lipopeptide antibiotic.

5. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core cyclic peptide of laspartomycin, zaomycin, crystallomycin, aspartocin, amphomycin, glumamycin, brevistin, cerexin A, cerexin B, Antibiotic A-30912, Antibiotic A-1437, Antibiotic A-54145, Antibiotic A-21978C or tsushimycin.

6. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core antibiotic of laspartomycin, zaomycin, crystallomycin, aspartocin, amphomycin, glumamycin, brevistin, cerexin A, cerexin B, Antibiotic A-30912, Antibiotic A-1437, Antibiotic A-54145, Antibiotic A-21978C or tsushimycin.

7. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core cyclic peptide of laspartomycin, aspartocin, Antibiotic A-30912, Antibiotic A-1437, Antibiotic A-54145 or Antibiotic A-21978C.

8. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core

antibiotic of laspartomycin, aspartocin, Antibiotic A-30912, Antibiotic A-1437, Antibiotic A-54145 or Antibiotic A-21978C.

9. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core cyclic peptide of laspartomycin or aspartocin.

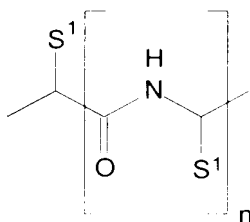
10. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core antibiotic of laspartomycin or aspartocin.

11. The antimicrobial sulfonamide derivative of Claim 4 in which m is 1.

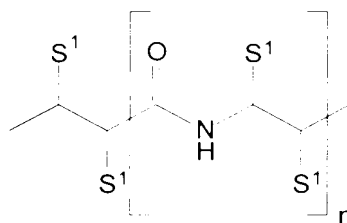
12. The antimicrobial sulfonamide derivative of Claim 4 in which R¹ and R⁴ are hydrogen.

13. The antimicrobial sulfonamide derivative of Claim 4 in which L is selected from the group consisting of:

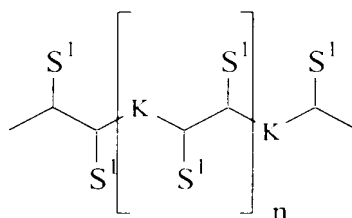
(L1)



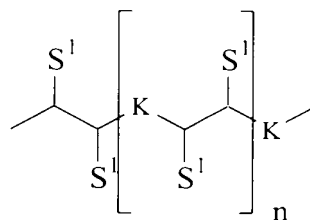
(L2)



(L3)



(L4)



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2 or 3;

each S^I is independently selected from the group consisting of hydrogen, (C₁-C₁₀) alkyl optionally substituted with one or more of the same or different R⁵ groups, (C₁-C₁₀) heteroalkyl optionally substituted with one or more of the same or different R⁵ groups, (C₅-C₁₀) aryl optionally substituted with one or more of the same or different R⁵ groups, (C₅-C₁₅) arylaryl optionally substituted with one or more of the same or different R⁵ groups, (C₅-C₁₅) biaryl optionally substituted with one or more of the same or different R⁵ groups, five to ten membered heteroaryl optionally substituted with one or more of the same or different R⁵ groups, (C₆-C₁₆) arylalkyl optionally substituted with one or more of the same or different R⁵ groups and six to sixteen membered heteroarylalkyl optionally substituted with one or more of the same or different R⁵ groups;

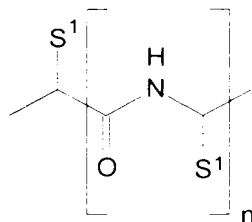
each R⁵ is independently selected from the group consisting of —OR⁶, —SR⁶, —NR⁶R⁶, —CN, —NO₂, —N₃, —C(O)OR⁶, —C(O)NR⁶R⁶, —C(S)NR⁶R⁶, —C(NR⁶)NR⁶R⁶, —CHO, —R⁶CO, —SO₂R⁶, —SOR⁶, —PO(OR⁶)₂, —PO(OR⁶), —CO₂H, —SO₃H, —PO₃H, halogen and trihalomethyl;

each R⁶ is independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, (C₅-C₁₀) aryl, five to sixteen membered heteroaryl, (C₆-C₁₆) arylalkyl and six to sixteen membered heteroarylalkyl; and

each K is independently selected from the group consisting of oxygen, nitrogen and sulfur.

14. The antimicrobial sulfonamide of Claim 13 in which each S^I is independently a side-chain of a genetically encoded α -amino acid.

15. The antimicrobial sulfonamide of Claim 13 in which L is:



16. The antimicrobial sulfonamide derivative of Claim 15 in which each S^1 is independently a side-chain of a genetically encoded α -amino acid.

17. The antimicrobial sulfonamide derivative of Claim 15 in which n is 0.

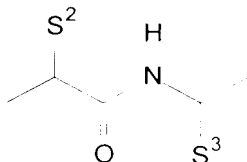
18. The compound of Claim 17 in which S^1 is hydrogen, Y^2 is decan-yl and R is the core cyclic peptide of aspartocin.

19. The antimicrobial sulfonamide derivative of Claim 17 in which S^1 is $-\text{CH}_2-\text{CO}_2\text{H}$, $-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{H}$, $-\text{C}(\text{OH})\text{H}-\text{CONH}_2$, $-\text{CH}_2-\text{CONH}_2$ or $-\text{CH}_2-\text{CH}_2-\text{CONH}_2$ or a salt or hydrate thereof.

20. The antimicrobial sulfonamide derivative of Claim 17 in which S^1 is $-\text{CH}_2$ -indol-2-yl or $-\text{CH}_2$ -phenyl.

21. The compound of Claim 20 in which R is the core antibiotic of laspartomycin and Y^2 is hexadecyl.

22. The antimicrobial sulfonamide derivative of Claim 13 in which L is:



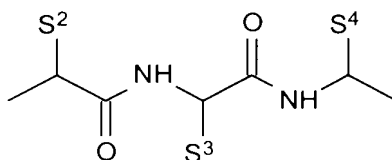
23. The antimicrobial sulfonamide derivative of Claim 22 in which S^2 and S^3 are

each independently a side chain of a genetically encoded α -amino acid.

24. The antimicrobial sulfonamide derivative of Claim 22 in which S^2 is hydrogen, $-\text{CH}_2\text{-indol-2-yl}$, $-\text{CH}_2\text{-CONH}_2$ or $-\text{CH}_2\text{-CH}_2\text{-CONH}_2$ and S^3 is $-\text{CH}_2\text{-CO}_2\text{H}$, $-\text{CH}_2\text{-CH}_2\text{-CO}_2\text{H}$ or a salt or hydrate thereof.

25. The antimicrobial sulfonamide derivative of Claim 22 in which S^2 is $-\text{CH}_2\text{-CO}_2\text{H}$, $-\text{CH}_2\text{-CH}_2\text{-CO}_2\text{H}$ or a salt or hydrate thereof and S^3 is $-\text{C(OH)H-CONH}_2$.

26. The antimicrobial sulfonamide derivative of Claim 13 in which L is:



27. The antimicrobial sulfonamide derivative of Claim 26 in which S^2 , S^3 and S^4 are each independently a side chain of a genetically encoded α -amino acid.

28. The antimicrobial sulfonamide derivative of Claim 26 in which S^2 is $-\text{CH}_2\text{-indol-2-yl}$, S^3 is $-\text{CH}_2\text{-CONH}_2$ or $-\text{CH}_2\text{-CH}_2\text{-CONH}_2$ and S^4 is $-\text{CH}_2\text{-CO}_2\text{H}$, $-\text{CH}_2\text{-CH}_2\text{-CO}_2\text{H}$ or a salt or hydrate thereof.

29. The antimicrobial sulfonamide derivative of Claim 26 in which S^2 is $-\text{CH}_2\text{-indol-2-yl}$, S^3 is $-\text{CH}_2\text{-CO}_2\text{H}$, $-\text{CH}_2\text{-CH}_2\text{-CO}_2\text{H}$ or a salt or hydrate thereof and S^4 is $-\text{CH}_2\text{-CONH}_2$, $-\text{CH}_2\text{-CH}_2\text{-CONH}_2$ or $-\text{C(OH)H-CONH}_2$.

30. The antimicrobial sulfonamide derivative of Claim 4 in which m is 0.

31. The antimicrobial sulfonamide derivative of Claim 30 in which R^1 is hydrogen.

32. The antimicrobial sulfonamide derivative of Claim 30 in which R is the core

antibiotic of laspartomycin or aspartocin.

33. The antimicrobial sulfonamide derivative of Claim 32 in which R is the core cyclic peptide of laspartomycin or aspartocin.

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34. A pharmaceutical composition comprising a compound according to Claim 4 and a pharmaceutically acceptable adjuvant, excipient, carrier or diluent.

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35. A method for treating or preventing a microbial infection, said method comprising the step of administering to a subject a therapeutically effective amount of a compound according to Claim 4 or a therapeutically effective amount of a pharmaceutical composition according to Claim 34.

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36. A method of inhibiting microbial growth, said method comprising the step of administering to a microbe an antimicrobially effective amount of a compound according to Claim 4 or an antimicrobially effective amount of a pharmaceutical composition according to Claim 34.

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37. A method for making an antimicrobial sulfonamide derivative comprising sulfonylating an core antibiotic or core cyclic peptide with a lipophilic sulfonyl derivative, thereby providing a antimicrobial sulfonamide derivative.

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38. The method of Claim 37 in which the lipophilic sulfonyl derivative is a activated lipophilic sulfonyl ester or a lipophilic sulfonyl halide.

39. The method of Claim 38 in which the activated lipophilic sulfonyl ester is a lipophilic hydroxybenzotriazole ester.

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40. The method of Claim 39 in which the lipophilic sulfonyl halide is a lipophilic sulfonyl chloride.

41. A method for making an antimicrobial sulfonamide derivative comprising:

sulfonylating a linker with a lipophilic sulfonyl compound, thereby providing a lipophilic sulfonamide linker; and

covalently attaching the lipophilic sulfonamide linker to an core antibiotic or core cyclic peptide, thereby yielding a antimicrobial sulfonamide derivative.

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42. A method for making an antimicrobial sulfonamide derivative comprising:

covalently attaching a linker to an core antibiotic or core cyclic peptide, thereby providing an linker core antibiotic or linker core cyclic peptide; and

sulfonylating the linker core antibiotic or linker core cyclic peptide with a lipophilic sulfonyl derivative, thereby yielding a antimicrobial sulfonamide derivative.

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